B2 Cont.

8. (Amended) ~~A cell culture~~ [Culture of cells, in particular of human origin, characterized ~~in~~ that they are] infected with the [adenovirus] adenoviral vector according to claim [7] 1.

REMARKS

Entry of the foregoing and favorable reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

In the Advisory Action dated August 4, 1998, the Examiner maintained the rejection of claims 1 and 3–8 under 35 U.S.C. § 103(a) as being unpatentable over *Rosenfeld et al.* taken with *Russell*, *Ramshaw et al.* and *Stratford–Perricaudet et al.*

In rendering this rejection, the Examiner purports that *Rosenfeld et al.* and *Stratford–Perricaudet et al.* teach the defective adenoviral vector of the present invention which lacks the transactivators E1A and E1B and the E3 region of the adenovirus. According to the Examiner, *Russell* provides the motivation to combine cytokines with alternate viral vectors for the treatment of cancer and *Ramshaw et al.* teaches the combination of an adenoviral vector containing genes encoding lymphokines. Therefore, the Examiner asserts that a skilled artisan would search for a new viral vector system to insert a gene coding for a cytokine for use in cancer therapy by the teachings of *Russell*, arrive at the teachings of *Ramshaw et al.* wherein the combination of an adenoviral vector and cytokine is taught and modify that vector to delete the E1 region.

However, Applicants submit that the Examiner's reliance on the primary reference of *Rosenfeld et al.* could only be through hindsight. To select among all of the vectors known in the art as of the filing date of the present invention and deem that an adenoviral vector would work could only be accomplished with the Applicants' claims in mind. Applicants further submit that a skilled artisan would start with the teachings of *Russell*, which suggests the use of other vectors in conjunction with a cytokine for cancer therapy, then proceed to *Ramshaw et al.* which teaches a variety of viral vectors containing a nucleotide sequence encoding a cytokine and then further proceed to alter this vector via the teachings of *Rosenfeld et al.* for cancer therapy since *Stratford–Perricaudet et al.* teaches many uses for these vectors.

However, Applicants submit that there is simply no guidance nor any expectation of success given to the skilled artisan to choose the presently claimed vector from those known in the art to treat tumors *in vivo*. Indeed, the problems associated with treating tumors are different

from the problems associated with treating a gene deficiency as will be discussed more extensively below.

First of all, it is well known in the case law that to prove a *prima facie* case of obviousness, not only a suggestion to modify is required in the combination of prior art references, but also there must be some suggestion in the combination of the prior art references of an expectation of success or the desirability of the combination. See, *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988) and *Also Standard Corp. v. Tennessee Valley Authority*, 808 F.2d 1490, 1 USPQ2d 1337 (Fed. Cir. 1986). This is clear from *In re Dow Chemical Co., supra* where the court stated the following:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art . . . Both suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure . . .

Therefore applying the above to *Russell*, it can be said that this reference does not suggest any expectation of success or desirablity to use defective viral vectors expressing a cytokine to treat tumors. Rather, *Russell* discourages, as Applicants have previously pointed out, the use of this type of vector and appears to encourage competent viral vectors.

It is clear in the case of *In re Dow Chemical Co., supra*, that negative teachings of the belief that the invention could not be made were also considered pertinent to the court. More specifically it was held that:

> the PTO erred in rejecting as *prima facie* obvious in view of the prior art the subject matter of the claims under reexamination relating to an impact resistant rubber–based resin having improved resistance to heat distortion; the prior art reflected a belief that the claimed products could not successfully be made by the use of the processes in the references cited as the basis for the rejection; the PTO's theory that one of ordinary skill would have found it "obvious to experiment" with the referenced processes is not a proper standard for obviousness (emphasis added).

Although *Russell* teaches the skilled artisan that genetic cytokine therapies and viral vector–mediated delivery was in the forefront, this reference also teaches that large hurdles had to be overcome prior to accomplishing this form of therapy. Furthermore, *Russell* suggests that defective viral vectors would not be successful when he clearly states:

> However, it is difficult to imagine how the problem of access to poorly vascularized tumour regions could be overcome except by the use of replication competent viruses . . .

This teaching also has to be considered and cannot be ignored, even though there is a general teaching that the feasibility of tumour targeted lymphokine gene therapy may be promising depending on whether a suitable vector can be found.

Even if a skilled artisan would look for alternative vectors that may be successful to treat tumors *in vivo* why would a skilled artisan choose an adenoviral vector when other vectors were known in the art?

For example, *Ramshaw et al.* teaches that several different types of vectors were known in the art at the critical filing date of the present invention. The disclosed vectors include vaccinia virus vectors, adenovirus vectors, poxvirus vectors, herpes virus vectors or bacterial vectors. *Ramshaw et al.* teaches in the examples, recombinant viral vectors encoding a cytokine gene using competent vaccinia virus, as well as a competent adenovirus. There is no suggestion that the adenovirus vector taught in *Ramshaw et al.* has any superior qualities over the vaccinia virus vector. In fact, all of the scientific data to illustrate that the invention works is done with the vaccinia virus.

Therefore, there is no suggestion to the skilled artisan that a competent adenoviral vector is more desirable to treat tumors *in vivo*. Nor is there any suggestion to modify the adenoviral vector of *Ramshaw et al.* to exclude the E1 region.

The Examiner relies on *Rosenfeld et al.* to deem that a skilled artisan would proceed to modify further the vector of *Ramshaw et al.* to delete the entire E1 region due to the following statement therein:

> Most human adults have antibodies to one of the three serogroup C adenoviruses to which Ad5 belongs (5). This implies little risk for those working with these vectors but may have negative implications for the virus as a gene transfer vector in the human lung. If such problems are encountered, alterations in the vector construct may be helpful.

Thus, the Examiner maintains that since it was known in the art that the E1 region is responsible for replication, the skilled artisan would delete this entire region.

Applicants disagree with the Examiner's interpretation of this teaching in *Rosenfeld et al.* This paragraph basically teaches the skilled artisan that due to the fact that most human adults have antibodies to adenoviruses, repeated administration of the vector may result in the antibodies "killing" the administered adenovirus and hence leaving the vector ineffective for therapeutic purposes, but having little risk for those working with the virus. Thus, in case the

adenovirus is "killed" by antibodies, *Rosenfeld et al.* suggests that by altering the vector construct may be helpful to solve this problem.

Altering does not necessarily mean deleting, as the Examiner suggested. Rather this definition means basically to change the adenoviral construct. However, no suggestion of how to change the construct is set forth in *Ramshaw et al.* nor *Rosenfeld et al.*

The Examiner's contention that the skilled artisan would interpret this suggestion to mean to delete the entire E1 region would in fact probably no solve the problem concerning the "killing" of the adenovirus via human antibodies, since the E1 regions, is not within the capside of the virus. Therefore, the skilled artisan would not be lead to delete the entire E1 region, as the Examiner maintains by the teachings of *Rosenfeld et al.*

Stratford–Perricaudet et al. fail to teach or suggest using an adenoviral vector to treat tumors *in vivo*. Rather, this entire reference suggests the use of adenoviral vectors to treat gene deficiencies.

Thus, the combination of references does not suggest to the skilled artisan to use the claimed defective adenoviral vectors to treat tumors *in vivo*. The only cited reference of record that teaches tumor therapy is *Russell* and this reference encourages the use of competent viral vectors and teaches away from the use of defective viral vectors.

Enclosed is a Declaration executed by Majid Mahtali that details more of the points set forth above.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Respectfully submitted,

MERCHANT, GOULD, SMITH, EDELL
WELTER & SCHMIDT, P.A.
3100 Norwest Center
90 South Seventh Street
Minneapolis, Minnesota 55402
(612) 332-5300

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Mark T. Skoog
Reg. No. 40,178
MTS:PSTlls